Furthermore, the significance of applicants' invention was discussed in Kubbatat and Vousdan ("Kubbatat"), submitted herewith. At page 251, Kubbatat discusses the role calpain plays in p53 degradation and the use of calpastatin to inhibit calpain in order to alter p53 levels. These statements, and the references cited for them, including Pariat (noted above), demonstrate that the use of calpain inhibitors to affect p53 levels is understood by one of skill in the art. The Carafoli *et al.* document, submitted herewith, also discusses the calpain degradation of p53 (at page 197) and the involvement in apoptosis (at page 198).

The Carafoli document also discusses numerous calpain inhibitors that one of skill in the art was familiar with (*see* page 194) and specifically discusses the fragments of calpastatin, for example the "conserved B regions," that one of skill in the art was familiar with. In addition, reference 32 of Carafoli (noted at page 194) is Maki *et al.* (of record), which discusses a 27 amino acid peptide corresponding to exon 1B, which is a strong inhibitor of calpain. Clearly, one skilled in the art could have selected and used any one of a variety of calpain inhibitors.

The Atencio *et al.* document, submitted herewith, demonstrates that the applicants' claims to utility and enablement of their invention in tumor cells in particular are correct (*see* page 4, lines 3-8). This document discusses how calpain inhibitors affect p53 levels and the apoptotic pathways associated with p53 (*see*, for example, pages 250-251, where activation of caspases is linked to calpain inhibition). As one of skill in the art knows, the relevance of p53 to apoptotic pathways in cells was know at the filing date of applicants' application. In addition, while not the most direct evidence, Atencio shows that adenoviral vectors can be routinely used to deliver genes and express polypeptides in tumor cells, which one of skill in the art would not question (*see* reference to rAd-p53, which was routinely used to express p53 protein in cells).

Applicants respectfully request consideration of this evidence and submit a PTO Form 1449 listing each document.

In the Office Action of December 19, 2001, there was one rejection to the previous claims. Applicants below fully and completely respond to that rejection and, to the extent it applies to the new claims, request its withdrawal.

The Rejection Under 35 U.S.C. § 112, First Paragraph

1. Written Description

Previous claims 21-22 and 28-29 were rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly fails to provide an adequate written description of the claimed invention. In particular, the PTO asserts that a description of "parts" of calpastatin that inhibit the activity of calpain is lacking (*see* page 2 of the Office Action). Applicants respectfully disagree.

Applicants have already shown, in the Reply filed March 19, 2002 (at pages 2-4, specifically incorporated herein by reference), that the specification describes a variety of types of inhibitors of calpastatin that could be used in the claimed methods and vectors. Applicants also assert that one of skill in the art could have routinely selected a calpain inhibitor, such as one of those noted in the documents discussed above, and used that inhibitor once applicants disclosed this invention. Thus, not only have applicants described a variety of calpain inhibitors, one of skill in the art would have immediately recognized the scope of compounds the term "calpain inhibitor" means in the art. Applicants have also shown in the last Response how the original claims evidence applicants' possession of the variety of inhibitors of calpain. Furthermore, the inclusion of a particular "part" of SEQ ID NO: 1 that is specifically listed as SEQ ID NO: 3 or 4, for example, represents unequivocal evidence of a description of "parts" of calpastatin that one of skill in the art understands.

As discussed in the Reply filed September 28, 2001, specifically incorporated herein by reference, applicants have met the written description requirement set forth in both the Patent Office Guidelines (66 FR 1099 (Jan. 5, 2001) ("Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1, 'Written Description' Requirement") and the relevant cases.

Applicants request reconsideration and withdrawal of this rejection if it is applied to the new claims.

2. Enablement

Previous claims 18-29 were rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly fails to contain a description of subject matter that enables one skilled in the art to make and/or use the invention claimed. Applicants respectfully disagree.

Applicants have shown previously, with arguments and supporting evidence (*see* Reply dated September 28, 2001, specifically incorporated herein by reference) how calpastatin, fragments of calpastatin, and inhibitors of the activity of calpain can be selected and used to regulate p53 levels and inhibit p53 degradation. The numerous documents discussed at the beginning of this paper also refer to and evidence the inhibition of calpain and its utility as asserted by applicants' specification. It would appear that all the evidence shows that applicants have correctly described methods and vectors that can be used to inhibit p53 degradation in a cell, while no evidence would cause one of skill in the art to question applicants' evidence or assertions.

Accordingly, applicants submit that a *prima facie* case of lack of enablement has not been made and/or has not been substantiated with adequate evidence. As noted in the previous Reply of March 19, 2002, and in the Reply filed September 28, 2001 (both incorporated herein by reference), when the appropriate standard is applied, applicants' claims would be allowed. Applicants' discussion above of the scientific merit in applicants' approach to p53 modulation and the inhibition of p53 degradation further evidences the allowability of the claims. Applicants respectfully assert that, applying the appropriate standards, one of skill in the art would believe that applicants have enabled the claimed invention.

This rejection should be withdrawn.

This application is now in condition for allowance. If the Examiner believes that prosecution might be furthered by discussing the application with applicant's representative, in person or by telephone, we would welcome the opportunity to do so.

Applicants believe that no extension of time fees, requests for extension of time, petitions, or additional claim fees are necessary to enter and consider this paper or keep this application pending. If, however, any extensions of time are required or any fees are due in order to enter or consider this paper or enter or consider any paper accompanying this paper, including fees for net addition of claims, applicants hereby request any extensions or petitions necessary and the Commissioner is hereby authorized to charge our Deposit Account # 50-1129 for any fees. If there is any variance between the fees submitted and any fee required, including the extension of time fee and fee for net addition of claims, the Commissioner is hereby authorized to charge or credit Deposit Account No. 50-1129.

Applicants have filed a Request for Continued Prosecution Application herewith. If the Patent Office determines a Request for Continued Examination is required, applicants hereby request that a Request for Continued Examination be entered, that the Response be considered, and the undersigned authorizes the Commissioner to deduct any fees from Deposit Account no. 50-1129.

Respectfully submitted,
Wiley Rein & Fielding LLP

Date: October 21, 2002

By: _____
David J. Kulik Reg. No. 36,576

Wiley Rein & Fielding LLP
Attn: Patent Administration
1776 K Street NW
Washington, D.C. 20006
Telephone: 202.719.7000
Facsimile: 202.719.7049

WRFMAIN 1180000.1